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Abstract—Isolated systolic hypertension is a common condition in individuals aged older than 60 years. However, isolated systolic hypertension has also been described in young individuals, although the mechanisms are poorly understood. We hypothesized that in young adults, isolated systolic hypertension and essential hypertension have different hemodynamic mechanisms and the aim of this study was to test this hypothesis in a cohort of subjects from The ENIGMA Study. Peripheral and central blood pressure, aortic pulse wave velocity, cardiac output, stroke volume, and peripheral vascular resistance were determined in 1008 subjects, aged 17 to 27 years. Compared with normotensive subjects, those with isolated systolic hypertension had significantly higher peripheral, central, and mean blood pressure, aortic pulse wave velocity, cardiac output, and stroke volume ($P < 0.001$ for all comparisons). However, there were no differences in pulse pressure amplification, heart rate, or peripheral vascular resistance between the two groups. Compared with subjects with essential hypertension, mean pressure, heart rate, and peripheral vascular resistance were all significantly lower in isolated systolic hypertensive subjects, but pulse pressure amplification, aortic pulse wave velocity, cardiac output, and stroke volume were higher ($P < 0.001$ for all comparisons). We have demonstrated that in young adults, isolated systolic hypertension and essential hypertension arise from different hemodynamic mechanisms. Isolated systolic hypertension appears to result from an increased stroke volume and/or aortic stiffness, whereas the major hemodynamic abnormality underlying essential hypertension is an increased peripheral vascular resistance. Long-term follow-up of these individuals is now required to determine whether they are at increased risk compared with age-matched normotensive individuals. (*Hypertension*. 2005;46:221-226.)

Key Words: arterial stiffness ■ hemodynamics ■ isolated systolic hypertension ■ stroke volume ■ young adults

Hypertension is a common disorder, affecting $\approx 25\%$ of the overall population^{1,2} and is a major risk factor for cardiovascular disease. Epidemiological data^{2,3} not only show an age-related change in the incidence of hypertension but also in its form. In those aged younger than 50, the predominant form of hypertension is essential hypertension (EH), involving elevation of systolic (SBP) and diastolic pressure (DBP), or DBP alone, which is characterized by increased peripheral vascular resistance (PVR). However, in older individuals, the most common form of hypertension is isolated systolic hypertension (ISH). This affects $\approx 50\%$ of those aged older than 60⁴ and, in contrast to EH, is thought to be caused mainly by large artery stiffening, resulting from disruption and fatigue–fracture of elastic fibers. Therefore, ISH is often considered to be an exaggeration of “normal” age-related stiffening seen in most populations. Indeed, we⁵ and others⁶ have shown that aortic pulse wave velocity (PWV), a measure of arterial stiffness, is increased in patients with ISH compared with age-matched controls.

Interestingly, data from a number of studies suggest that ISH is also prevalent in adolescents⁷ and young adults.⁸ Although the mechanisms underlying ISH in younger individuals are poorly understood, two recent reports suggest that exaggerated pulse pressure (PP) amplification may be responsible and, hence, the terms “pseudo” or “spurious” hypertension have been applied.^{9,10} However, in both studies, central PP appeared to be elevated in the ISH subjects compared with normotensive individuals, suggesting that ISH in young individuals may not be benign. Moreover, neither study assessed cardiac output (CO) nor aortic stiffness, the principal determinants of PP.

We hypothesized that in young adults, ISH and EH result from different hemodynamic mechanisms and, specifically, that ISH results primarily from increased CO and/or aortic stiffening, rather than increased PVR. The aim of the present study was to test this hypothesis in a large cohort of healthy young subjects from The ENIGMA Study.

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From Clinical Pharmacology Unit (C.M.M., Y., S.W., K.M.-P., M.J.B., I.B.W.), University of Cambridge, Addenbrooke’s Hospital, Cambridge, UK; Wales Heart Research Institute (B.M., J.E.S., Y., S.W., R.C.L., J.R.C.), Cardiff University, University Hospital, Cardiff, UK; Department of Medicine (S.S.F.), University of California, Irvine, Calif; and School of Applied Sciences (C.R.), University of Glamorgan, Pontypridd, UK.

Correspondence to Dr Carmel McEniery, Clinical Pharmacology Unit, University of Cambridge, Addenbrooke’s Hospital Box 110, Cambridge, CB2 2QQ, UK. E-mail cmm41@cam.ac.uk

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Methods

The ENIGMA Study is a long-term follow-up study of young individuals, investigating the origins of hypertension with regard to clinical, physiological, and genetic characteristics. The initial screening cohort consisted of 1668 individuals, selected at random from two University populations in the UK (Cambridge and Wales; response rate $\approx 70\%$). Detailed hemodynamic measurements were then recorded in 1028 randomly scheduled subjects. Subjects with diabetes mellitus, a serum cholesterol ≥ 6.5 mmol/L, renal disease, or cardiovascular disease were excluded, as were subjects receiving any medication, leaving 1008 individuals for the present analyses. Approval for all studies was obtained from the Local Research Ethics Committees, and written informed consent obtained from each participant.

Protocol

All subjects completed a detailed lifestyle and medical history questionnaire, and height and weight were assessed. After 15 minutes of seated rest, brachial BP and radial artery waveforms were recorded. After 20 minutes of supine rest, brachial BP and radial artery waveforms were re-assessed, and PWV and CO were determined, as described.

Hemodynamics

Brachial BP was recorded in the dominant arm using a validated oscillometric technique (HEM-705CP; Omron Corporation).¹¹ Readings were taken in duplicate, or triplicate if readings differed by >5 mm Hg. Radial artery waveforms were recorded with a high fidelity micromanometer (SPC-301; Millar Instruments) from the wrist of the dominant arm, and pulse wave analysis (SphygmoCor; AtCor Medical) was used to generate a corresponding central (ascending aortic) waveform, as validated previously.¹² From this, central BP, augmentation index (AIx), mean arterial pressure (MAP), and heart rate (HR) were calculated, as described previously.¹³ Carotid–femoral (aortic) and carotid–radial (brachial) PWV were recorded using the same device, as described previously.¹³ Carotid waveforms were rescaled to the MAP and DBP to allow carotid AIx and SBP to be calculated, without the use of any radial to aortic transfer function.¹⁴ Cardiac output was assessed using a noninvasive, inert gas rebreathing technique.¹⁵ Briefly, while resting, subjects continuously rebreathed a gas mixture (1% SF₆, 5% N₂O, and 94% O₂) over 20 seconds, with a breathing rate of 15/min. Expired gases were sampled continuously and analyzed by an infrared photoacoustic gas analyser (InnoCor; Innovision A/S) for the determination of CO and stroke volume (SV). All measurements were made by trained investigators. The within-observer and between-observer measurement reproducibility values for the arterial stiffness measurements were in agreement with our previously published data.¹³ The coefficient of variation of repeated determinations of cardiac output was $<10\%$.

Data Analysis

Data were analyzed using SPSS software (version 11.0). Subjects were grouped into 4 categories, according to seated peripheral BP: normotensive (SBP <130 mm Hg and DBP <85 mm Hg); high-normal (SBP 130 to 139 mm Hg and/or DBP 85 to 89 mm Hg); ISH (SBP ≥ 140 mm Hg and DBP <90 mm Hg); and EH (SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg). Data were analyzed using one-way analysis of co-variance (ANCOVA), with gender included as a covariate. Post hoc analyses were conducted using the Bonferroni method. Individuals with high-normal BP were excluded from these analyses to reduce the potential for confounding overlap between the groups.

Stepwise linear regression was used to investigate independent determinants of hemodynamic variables. Independent variables were chosen based on simple correlation analyses or those known or likely to be associated with the parameters under study. All values represent means \pm SD, and $P < 0.05$ was considered significant.

TABLE 1. Characteristics of the Entire Study Cohort (N=1668), Grouped According to Seated BP

Category	Males		Females	
	No.	Age	No.	Age
Normotensive	470	20 \pm 6	705	20 \pm 6
High-normal	206	20 \pm 6	79	18 \pm 8
Isolated systolic hypertension	109	19 \pm 7	21	20 \pm 6
Essential hypertension	35	20 \pm 6	43	23 \pm 6
Total	820	20 \pm 6	848	19 \pm 7

Normotensive indicates optimal and normal BP (JNC VI guidelines¹⁶); essential hypertension, increased SBP and/or increased DBP, on the basis of the first screening examination.

Results

Table 1 shows the mean age and gender of all 1668 subjects, grouped according to seated BP at the first screening examination. The overall prevalence of hypertension, regardless of its form, was 12%, (ISH 8%, $n=130$; and EH 4%, $n=78$). Raised BP was confirmed using JNC IV guidelines¹⁶ in 68% of subjects with ISH and 77% of subjects with EH, either by 24-hour ambulatory BP monitoring, or ≥ 3 seated BP readings over several months.

Hemodynamics According to BP Category

Detailed hemodynamic measurements, made in 1008 subjects, are listed in Table 2, excluding subjects with high-normal BP ($n=151$). There were no differences in age, number of smokers, family history of hypertension, or exercise habits between the 3 groups. However, compared with normotensive subjects, ISH subjects were taller, heavier, had a higher body mass index (BMI), and were more likely to be male. Compared with the EH group, ISH subjects were taller, but not heavier, and there was no difference in BMI. However, the EH group contained a significantly higher proportion of females. Secondary analyses, based on male subjects, confirmed the group differences in height and weight.

Hemodynamic variables are shown in Table 3. Compared with normotensive subjects, subjects with ISH had significantly higher peripheral and central SBP, DBP, PP, and MAP. There were no differences in PP amplification, HR, brachial PWV, or PVR between ISH and normotensive subjects. However, subjects with ISH did have a significantly higher aortic PWV, CO, and SV, and lower AIx.

Compared with subjects with EH, MAP, HR, AIx, brachial PWV, and PVR were all significantly lower in ISH individuals, but peripheral and central PP, PP amplification, aortic PWV, CO, and SV were higher. The differences in CO and SV between the groups persisted when corrected for body surface area. In addition, substituting carotid SBP and AIx as surrogate central indices (ie, without using a transfer function), did not meaningfully alter any of the results.

Factors Influencing Hemodynamic Indices

Stepwise multiple regression models were constructed using all 1008 subjects to determine the factors influencing PP, aortic PWV, and SV (Table 4). Although gender emerged as the most

TABLE 2. Demographics and Blood Pressure Indices in Normotensive, ISH, and EH Subjects

Parameter	Normotensive (n=722)	ISH (n=93)	EH (n=42)	ANCOVA P
Age, years	20±3	20±3	20±3	0.8
Age range	17–27	17–25	17–26	
Gender, male/female	330/392	85/8	23/19	
Height, m	1.71±0.09	1.79±0.07*	1.70±0.09*†	<0.001
Weight, kg	68±13	82±14*	75±17*	<0.001
BMI, kg/m ²	23.1±3.6	25.7±4.1*	25.8±4.6*	<0.001
Smoker, %	28	15	25	0.1
Family history of HT, %	22	28	36	0.1
Exercise, %	83	84	75	0.4
Peripheral SBP, mm Hg	115±9	146±5*	141±9*†	<0.001
Peripheral DBP, mm Hg	71±7	78±7*	95±6*†	<0.001
Peripheral PP, mm Hg	44±9	66±7*	46±9†	<0.001
MAP, mm Hg	85±7	99±6*	111±7*†	<0.001
Central SBP, mm Hg	98±8	120±6*	125±8*†	<0.001
Central DBP, mm Hg	71±7	78±7*	95±6*†	<0.001
Central PP, mm Hg	27±5	42±5*	30±6*†	<0.001
HR, bpm	68±11	69±12	75±10*†	<0.001

Data are means±SD (n=857). Subjects with high-normal BP excluded (n=151).

Smoker, % indicates the proportion of each group who smoke ≥1 cigarette per day; exercise, %, the proportion of each group who undertake exercise ≥3 times per week, based on self-reported habits; family history of HT, the proportion of each group having an immediate family member (parent or sibling) diagnosed by a medical practitioner as hypertensive.

Data were analysed using univariate ANCOVA, with gender as a covariate. Post hoc comparisons were made using the Bonferroni method. *P<0.01 vs normotensives. †P<0.01, EH vs ISH.

important determinant of PP, SV and aortic PWV were also independently associated with both peripheral and central PP. As expected, MAP had the strongest association with PWV, followed by age, gender, and HR. In contrast, height, weight, and HR were the strongest determinants of SV, with MAP, gender, and ejection duration exerting a small but significant influence.

Physiological Determinants of ISH

Subjects were stratified into quartiles of SV and aortic PWV to investigate their influence on PP (Figure 1). There was a significant increase in peripheral PP from the lowest to the highest quartiles of both SV and PWV (P<0.001). For a

given level of PWV, PP increased moving up quartiles of SV, and vice versa. A similar effect was also observed for central PP. To investigate further the hemodynamic patterns within the ISH group, they were divided into high or low SV and PWV, based on the mean values of the normotensive group (Figure 2). Stroke volume was elevated above the normotensive mean in 69% of subjects with ISH, and PWV was higher than the normotensive mean in 61%. The demographic and hemodynamic characteristics of the ISH subgroups are compared in Table 5, which indicate that 28% had a primary elevation of SV, 20% had a primary elevation of PWV, and 41% had an elevation of both PWV and SV.

TABLE 3. Hemodynamic Variables in Normotensive, ISH, and EH Subjects

Parameter	Normotensive (n=722)	ISH (n=93)	EH (n=42)	ANCOVA P
PP Amplification§	1.69±0.14	1.72±0.11	1.63±0.2*†	<0.001
Alx, %§	0±12	-4±12*	5±13*†	<0.001
Brachial PWV, m/s§	7.18±1.07	7.09±1.06	7.96±1.04*†	<0.001
Aortic PWV, m/s§	5.83±0.32	6.26±0.39*	6.00±0.45†	<0.001
CO, L/min§	6.9±1.9	8.1±1.9*	6.8±1.7†	<0.001
SV (ml) §	83±21	93±24*	78±18†	<0.001
PVR, dynes/s§	12.6±4.6	12.5±3.4	15.9±4.3*†	<0.001

Data are means±SD (n=857). Subjects with high-normal BP excluded (n=151).

§ indicates data corrected for MAP and gender.

Data were analysed using univariate ANCOVA, with gender as a covariate. Post hoc comparisons were made using the Bonferroni method. *P<0.01 vs normotensive. †P<0.01, EH vs ISH.

TABLE 4. Stepwise Regression Analyses

Model	Regression Coefficient	SE	β	<i>P</i>	R ² Change (%)
Peripheral Pulse Pressure R ² = 0.46, <i>P</i> < 0.001					
Gender	-0.89	0.91	-0.44	0.001	37
Stroke volume	0.14	0.02	0.28	0.001	6
Alx	-0.13	0.04	-0.14	0.001	2
Aortic PWV	3.24	1.01	0.13	0.001	2
Age	-0.35	0.16	-0.08	0.034	1
Central Pulse Pressure R ² = 0.42, <i>P</i> < 0.001					
Gender	-5.51	0.59	-0.43	0.001	32
Stroke volume	0.09	0.01	0.030	0.001	6
Aortic PWV	2.07	0.65	0.13	0.002	3
Alx	0.07	0.02	0.12	0.003	2
Aortic PWV R ² = 0.23, <i>P</i> < 0.001					
MAP	0.03	0.01	0.37	0.001	17
Age	0.04	0.001	0.18	0.001	2
Gender	-0.24	0.06	-0.15	0.001	2
HR	0.01	0.003	0.14	0.001	2
Stroke Volume R ² = 0.47, <i>P</i> < 0.001					
Height	62.27	9.89	0.27	0.001	33
Weight	0.55	0.06	0.35	0.001	8
HR	-0.30	0.07	-0.15	0.001	5
MAP	-0.20	0.08	-0.08	0.011	1
Gender	-5.68	1.83	-0.13	0.002	1
Ejection duration	0.08	0.04	0.07	0.045	1

Stepwise linear regression analyses using all 1008 subjects. The regression coefficient provides the slope of the regression line, and β provides a measure of the relative strength of the association independent of the measurement units. Dependent variables are shown in bold.

Discussion

The aim of the current study was to investigate the mechanisms of hypertension and, particularly, ISH in young adults by studying a large cohort of subjects from The ENIGMA Study. We have confirmed that ISH is the most common form of hypertension in young adults, outnumbering EH by a ratio of

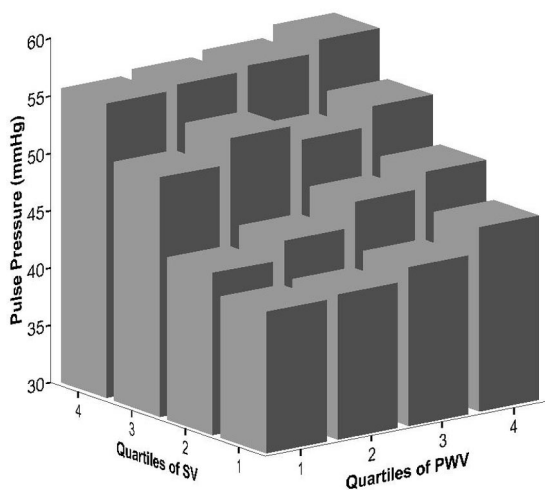


Figure 1. Influence of SV and aortic PWV on peripheral PP.

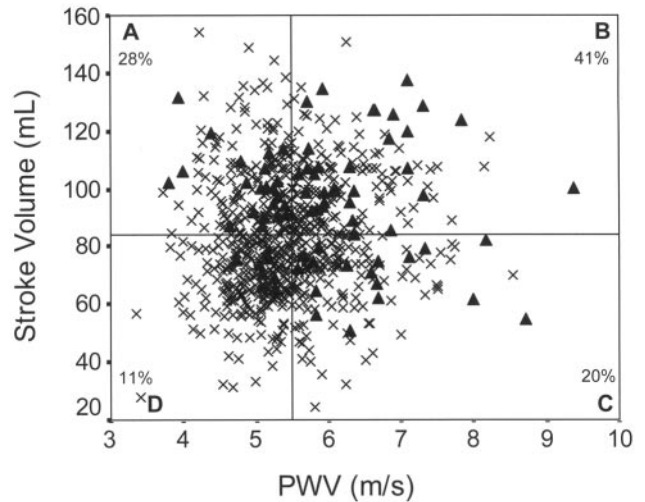


Figure 2. Scatterplot of SV versus aortic PWV in normotensive (-X-) and ISH (-%) subjects. The crossbars represent the normotensive means for SV (horizontal) and PWV (vertical). A indicates upper SV, lower PWV; B, upper SV, upper PWV; C, lower SV, upper PWV; and D, lower SV, lower PWV. Percentages within the graph represent the proportion of subjects within each quadrant, as shown in Table 5.

≈2:1. The major new findings are that ISH and EH have different underlying hemodynamic mechanisms. Our data demonstrate that ISH in young adults is a heterogeneous condition, involving elevations of SV or aortic stiffness and, in some individuals, disturbances of both, but PP amplification is normal. In contrast, the predominant hemodynamic abnormality in EH was an elevated PVR, and a decreased SV, but normal isobaric aortic stiffness and reduced PP amplification.

Previous epidemiological studies in young adults⁸ and in adolescents⁷ show a similar preponderance of ISH over EH as observed in the current study. However, the hemodynamic mechanisms underlying ISH in young individuals have not been studied extensively. Two recent reports^{9,10} hypothesized that ISH may result from exaggerated amplification of a “normal” central PP. However, in the current study, there was no difference in PP amplification between subjects with ISH and normotensives. Central SBP was ≈22 mm Hg higher in ISH versus normotensives, suggesting that ISH in young individuals is not a problem of amplification and might not be benign, in contrast to previous suggestions.^{9,10,17} Conversely, SV and/or aortic PWV were increased in the majority of subjects with ISH (89%), compared with normotensive individuals. Interestingly, a recent study in young individuals¹⁸ demonstrated that a high PP was positively associated with an elevated SV, although this was a small study and data on aortic stiffness were not provided.

In contrast to ISH, the individuals with EH mirrored the “classical” picture described in earlier studies^{19–21} with a significantly increased PVR and reduced SV. Previous investigators^{22–25} also described the phenomenon of a hyperdynamic circulation in young individuals, preceding the development of “classical” EH, characterized by normal PVR but increased SV and/or HR. Clearly, some of the ISH subjects identified in the current study fit this description, with elevated SV (group A), or elevated SV and PWV (group B) and may well progress to develop EH, with an increased PVR and reduced SV. However,

TABLE 5. Comparison of Subject Characteristics and Hemodynamics in ISH Subjects, Grouped According to Level of SV and Aortic PWV

Quadrant of Stroke Volume/PWV % of Total	A Upper SV/ Lower PWV 28%	B Upper SV/ Upper PWV 41%	C Lower SV/ Upper PWV 20%	D Lower SV/ Lower PWV 11%	ANOVA <i>P</i>
Gender, % male	96	91	88	89	0.8
BMI, kg/m ²	25±3	26±4	27±5	24±3	0.3
Peripheral SBP, mm Hg	147±4	146±4	148±7	145±4	0.6
Peripheral DBP, mm Hg	74±8	80±6	84±4	79±7	0.008
MAP, mm Hg	97±7	100±6	104±5	99±7	0.01
Central SBP, mm Hg	118±6	120±6	123±7	118±4	0.06
Central DBP, mm Hg	74±8	80±6	84±4	79±7	0.007
PP amplification	1.75±0.07	1.72±0.12	1.73±0.12	1.79±0.10	0.4
HR, beat/min	66±2	65±10	70±14	69±10	0.012
Aortic PWV, m/s*	5.05±0.48	6.33±0.79	6.43±0.94	5.22±0.6	<0.001
CO, L/min	8.87±1.24	9.53±1.62	6.46±1.57	5.1±0.2	<0.001
SV, mL	101±11	106±15	69±9	71±5	<0.001
PVR, dynes/s	10.7±1.7	10.1±1.9	16.3±5.0	12.9±3.1	<0.001

Data are means±SD. *Data corrected for MAP. Data were analysed using ANOVA. There were no differences between groups in the No. of smokers or those undertaking regular exercise (>3×per week, based on self-reported exercise habits).

PVR indicates peripheral vascular resistance.

≈20% of subjects in the current study had normal SV but increased aortic PWV (group C), suggesting that ISH is a heterogeneous condition that, at least in some individuals, might be associated with premature aortic stiffening. These individuals appear to have the same pathophysiological mechanism underlying their hypertension as older ISH subjects. However, whether such stiffening is caused by age-related elastin degeneration is unclear, but this appears unlikely, suggesting that other mechanisms may be important. Interestingly, data from the Framingham Heart Study suggest that PP tracks throughout life and that individuals with a high PP aged 30 to 35 years are more likely to develop ISH later in life.²⁶ Therefore, subjects with elevated PP and aortic stiffening may be predisposed to ISH developing later in life and, as such, may represent the “tip” of the later ISH iceberg.

The mechanisms underlying the increase in SV and PWV among ISH subjects are unclear. Sorof et al²⁷ described an association between ISH in adolescence and increased BMI, as we did in our population. However, in the current study, SV remained significantly elevated in the ISH subjects, even when corrected for body surface area. The same authors also suggest that sympathetic nervous system hyperactivity might contribute to ISH in adolescence.²⁷ Such a mechanism may explain, at least in part, the increased SV and PWV observed in the current study. Moreover, in some individuals with elevated SV, an increase in sympathetic activation might prevent a compensatory decrease in PVR. However, HR was not elevated in the ISH subjects, compared with normotensive subjects, and, clearly, the hypotheses concerning sympathetic activity and ISH require further investigation. Other possible mechanisms underlying the increase in PWV may involve structural^{28–30} or functional^{31,32} factors regulating arterial stiffness.

Limitations

Although the overall prevalence of hypertension in the current study was ≈12%, data from NHANES III¹ suggests a

prevalence of ≈5% in a similar age group. This discrepancy may reflect the fact that baseline BP readings were taken on a single visit only, albeit in duplicate and after 15 minutes of seated rest. However, our data are comparable with those from the Health Survey for England,³³ which, based on single BP readings, gave a prevalence of hypertension of ≈10% in those <30 years. Nevertheless, we were able to confirm the diagnosis of hypertension in the majority of individuals, with regression to the mean and, to a lesser extent, white coat hypertension accounting for the remainder. An additional limitation is that our investigation of University students may bias our observations toward a healthy population. However, previous studies conducted in University populations suggest that the prevalence of hypertension is similar to those reported in NHANES I.^{34,35} Finally, although the cross-sectional nature of the current study allows us to characterize hemodynamic mechanisms underlying the different forms of hypertension in young individuals, this approach does not allow us to investigate the causal mechanisms, or to distinguish parallel from sequential pathways in the development of ISH. However, The ENIGMA Study is a long-term follow-up study, which should enable us to determine the causal mechanisms of hypertension in the future.

Perspectives

Hypertension is a major modifiable risk factor for cardiovascular disease. However, it is not a uniform condition and has distinct forms. Once established, hypertension is essentially incurable and thus patients are subjected to a lifetime of antihypertensive medication, with the potential for side effects and drug interactions. However, a better understanding of the hemodynamic changes contributing to the different forms of hypertension in young individuals, and their underlying mechanisms, may well allow us to intervene at an

earlier stage, with pharmacological or even nonpharmacological treatments. Treatments such as weight loss or strategies to reduce CO or sympathetic nervous system activity might prevent hypertension from becoming established, although clearly this hypothesis needs to be tested. However, only after long-term follow up of such individuals, will we be able to determine who ultimately develops EH or ISH later in life, or if any of these individuals regres to a normal BP.

Conclusion

We have demonstrated that in young adults, ISH and EH arise from different hemodynamic mechanisms. Isolated systolic hypertension appears to result from an increased SV and/or aortic stiffness, whereas the major hemodynamic abnormality underlying EH is an increased PVR. The mechanisms driving these hemodynamic changes are poorly understood and, clearly, further work is required to understand why some young individuals are more susceptible to the development of hypertension, regardless of its form.

Appendix

The Enigma Study Investigators are: Derin Balogun, Samantha Benedict, Ross Campbell, Edward Davidson, Zahid Dhakam, Rhiannon Edwards, Ian Hall, Patrick Harnett, Sian Howarth, Dai Lloyd, Isla Mackenzie, Maggie Munnery, Pawan Pusalkar, Michael Sansbury, Matthias Schmitt, Justin Taylor, Edna Thomas, Neil Thomas, Rachel Westcott, Olwyn Westwood, Simon Williams.

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